HED DOC. NO. 013989

DATE: August 10, 1999

MEMORANDUM

SUBJECT: **TRICHLORFON** AND **DICHLORVOS (DDVP):** REASSESSMENT OF THE REQUIREMENTS FOR THE PRENATAL DEVELOPMENTAL STUDIES IN GUINEA PIG - Report of the Hazard Identification Assessment Review Committee.

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and
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THROUGH: Jess Rowland, Co-Chair
And
Pauline Wagner, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Susan Hummel, Ph.D.
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PC Code 057901 and 084001

This report presents the Hazard Identification Assessment Review Committee's (HIARC) conclusions on the reassessment of the previous requirement by the HIARC of a prenatal developmental toxicity study in guinea pigs for Trichlorfon and DDVP.

Committee Members in Attendance

Members present: William Burnam, Virginia Dobozy, Karen Hamernik, Mike Ioannou, Tina Levine, Susan Makris, Nancy McCarroll, Nicole Paquette, Kathleen Raffaele, Jess Rowland, PV Shah, Pauline Wagner, and Brenda Tarplee (executive, secretary).

Member(s) in absentia: David Anderson and Pamela Hurley.

Data was presented by Abdullah Khasawinah of the Reregistration Branch 4 (RRB4).

Also in attendance were: Ray Kent and Susan Hummel of RRB4.

Data Presentation:
and
Report Preparation

Abdullah Khasawinah, Ph. D.

I. BACKGROUND

On May 7, 1998, the HIARC reviewed and evaluated a prenatal developmental toxicity study in guinea pigs published in the open literature by Mehl et al., 1994. In this study, Trichlorfon (125 mg/kg), DDVP (15 mg/kg, once or twice/day) and several other organophosphates (dimethoate, TOCP, Soman, and ethyl trichlorfon) were administered (route unspecified) to pregnant outbred albino guinea pigs (Ssc: AL, MOI:DHF) between day 42 and 46 of gestation. Trichlorfon caused significant decreases in total brain weight (29%), and significant decreases in cerebellum, medulla, thalamus/hypothalamus, the calyculi, and the cerebral cortex. DDVP produced significant decreases in total brain weight (12-14%) and significant decreases in cerebellum, medulla, thalamus/hypothalamus, and the calyculi. Based on these findings, the HIARC concluded that a developmental toxicity study in guinea pigs should be conducted with certain protocol modifications (including examination of brain weight) to replicate/confirm the findings of Mehl, et al., 1994 (HIARC Report dated June 8, 1998; HED Document No. 012629).

In response to the request, the Registrant (AMVAC, January 9, 1999) provided additional information regarding this study. AMVAC concluded that the study was inappropriate for regulatory decision because the route of dosing was subcutaneous, the study did not follow GLP nor did it have a quality assurance check, the animals were dosed over a period of years, different dosing regimens were used, and the animals were not observed further.

II. RESULTS OF THE DDVP HIARC RE-EVALUATION

On May 27, 1999, The HIARC reviewed AMVACs submission and acknowledged that the Mehl et al. study had limitations which raised doubts about the reliability of this study. Because of the deficiencies with Mehl et al. study and other factors (e.g., guinea pigs are not the common species for conducting developmental toxicity study as well as the lack of historical control data) the HIARC concluded that it may not be appropriate to conduct a developmental toxicity study in this species (guinea pigs). The HIARC, however, determined that a developmental neurotoxicity study in rats would be more appropriate since such a study would allow much broader evaluation of both the neuropathology following pre and post natal exposures as well as behavioral testing. Consequently, the HIARC withdrew the request for a developmental study with guinea pigs and, instead is requesting a developmental neurotoxicity study in rats (HIARC Report dated June 8, 1999; HED Document No 013247).

III. RESULTS OF THE TRICHLORFON HIARC RE-EVALUATION

On August 5, 1999, the HIARC, in light of the above DDVP decision, reviewed the data on trichlorfon in reference to the request for a developmental toxicity study with guinea pigs for this chemical. Following review of the published studies the HIARC noted that unlike DDVP in which the route of exposure was subcutaneous, the effects in guinea pigs and mini-pigs were seen following oral exposure of trichlorfon (Berge, GN. et al. 1986; 1987a and b; Hjelde, T; et al.1998; Knox, B. et al. 1978; Mehl, N. et al.1994 and Pope, A. et al. 1986). HIARC reiteriated its concern for the developmental effects seen with with these compounds since DDVP is the active metabolite of trichlorfon.

The HIARC determined that a developmental neurotoxicity study in rats would be more appropriate than a guinea pig developmental toxicity study for the same reasons discussed above

(deficiencies with Mehl et al. study and other factors - e.g., guinea pigs are not the common species for conducting developmental toxicity study as well as the lack of historical control data). Additionally, this decision would be consistent with that of the DDVP which is a structural analog and the active metabolite. Consequently, the HIARC withdrew the request for a developmental study with guinea pigs and, instead is requesting a developmental neurotoxicity study in rats .

The HIARC further concluded that in the future the Agency has the option to request additional studies in appropriate species for either compound, depending upon the results of the developmental neurotoxicity studies in rats and/or other relevant data identified from other sources.

IV. REFERENCES

Health Effects Division (HED) Documentation

HED Memorandum June 2, 1999. HED DOC. NO. 013435 Trichlorfon -Replacement of human study used in risk assessement- Report of the HIARC.

HED Memorandum June 3, 1998. HED DOC. NO. 012629 Dichlorvos DDVP - Reevaluation- Report of the HIARC.

HED Memorandum June 8, 1999. HED DOC NO. 013427 Dichlorvos DDVP - Reassessment of the Requirement for the Prenatal Developmental Toxicity Study in Guinea Pig- Report of the HIARC.

HED Memorandum May 3, 1999. From William Sette to Pamela Noyes. DDVP (084001): Response to AMVAC related to EPA's basis for concern for potential developmental neurotoxic effects and revised testing recommendation.

Published Prenatal Brain Developmental Studies

Berge, G.; Nafstad, I; Fonnum, F. 1986. Prenatal effects of trichlorfon on the guinea pig brain. Arch. Toxicol. 59:30-35.

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Mehl, N.; Schanke, T.; Johnsen, B.; Fonnum, F. 1994. The effect of trichlorfon and other organophospates on prenatal brain development in the guinea pig. Neurochem. Res. 19(5):569-574.

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